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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/321,655	05/28/1999	STANTON L. GERSON	CWR-7091NP	6848

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
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11/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/321,655	GERSON, STANTON L.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 9/5/08 was entered.

Amended claims 2-5 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

Upon further consideration and in light of Applicant's amendment and arguments, the rejection under 35 U.S.C. 102(b) as being anticipated by Reese et al. (Proc. Natl. Acad. Sci. 93:14088-14093, 1996) was withdrawn in favor of the remaining rejections. It is further noted that human bone marrow stroma was derived from bone marrow mononuclear cells that were passaged only **once** and irradiated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Nolta et al. (Blood 86:101-110, 1995, Cited previously) as evidenced by Prockop, D.J. (Science 276:71-74; Cited previously) for the same reasons already set forth in the Office action mailed 3/5/08 (pages 4-5) ***The same rejection is restated below.***

Nolta et al. disclosed a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of a stroma generated by human allogeneic bone marrow stromal cells which were irradiated and passaged prior to the plating of CD34 cells (Abstract, and column 1, page 102). The utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells (column 1, third paragraph, page 102), and it contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Nolta et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction by vigorous flushing and plating the collected cells twice to eliminate adherent stromal cells (column 1, last paragraph, page 102).

Accordingly, the method taught by Nolta et al meets every limitation of the claims as broadly written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 9/5/08 (pages 5-6) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicant argues basically that Nolta et al do not teach co-culturing human hematopoietic progenitor cells with **human mesenchymal stem cells isolated from human mesoderm tissue**. Applicant further argues that bone marrow human stroma is not equivalent to mesenchymal stem cells which have been isolated from human tissue; and that isolated MSCs are distinct in morphology and lack surface markers for T and B lymphocytes, macrophages and endothelial cells.

Firstly, please note that **the bone marrow stromal cell population** derived from bone marrow spicules **(after passage no. 4)** as taught by Nolta et al. **is devoid of most hematopoietic cells (column 1, third paragraph, page 102) and containing mesenchymal stem cells or multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop**. This bone marrow stromal cell population falls within the broad scope mesenchymal stem cells isolated from human mesoderm tissue.

Secondly, the claims do not require the mesenchymal stem cells that are isolated from human mesoderm tissue (e.g., bone marrow) **are homogenous or purified by any particular method**, so that no T and B lymphocytes, macrophages and endothelial cells are found. Please also note that the bone marrow stromal cell population of Nolta is devoid of most hematopoietic cells.

Thirdly, it is further noted that the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in**

Dexter stroma and FN enhanced transduction" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23).

Accordingly, amended claims 3-5 are still rejected under 35 U.S.C. 102(b) as being anticipated by Nolta et al. as evidenced by Prockop, D.J. for the reasons set forth above.

Amended claims 2 and 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Wells et al. (Gene therapy 2:512-520, 1995) as evidenced by Prockop, D.J. (Science 276:71-74; Cited previously) for the same reasons already set forth in the Office action mailed 3/5/08 (pages 5-6) ***The same rejection is restated below.***

Wells et al. disclosed a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with a retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of an autologous bone marrow stromal support containing passaged and irradiated adherent stromal cells depleted of hematopoietic cells and macrophages (see at least Abstract and Materials and Methods, particularly pages 518-519). The utilized bone marrow stromal support contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-

adherent cells. Wells et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction (column 1, first full paragraph, page 519).

Accordingly, the method taught by Wells et al meets every limitation of the claims as broadly written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 9/5/08 (pages 6-9) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Once again, applicant argues basically that Wells et al do not teach co-culturing human hematopoietic progenitor cells with **human mesenchymal stem cells isolated from human mesoderm tissue**. Applicant also argues that bone marrow human stroma is not equivalent to mesenchymal stem cells which have been isolated from human tissue; and that isolated MSCs are distinct in morphology and lack surface markers for T and B lymphocytes, macrophages and endothelial cells. Applicant further argues that although Prockop states that adherent marrow stromal cells have many of the characteristics of mesenchymal stem cells, Prockop also states "The cells, isolated by their adherence to plastic as described by Friedenstein (5), initially are heterogeneous and are difficult to clone. The fraction of hematopoietic cells is relatively high in initial cultures of mouse marrow but is less than 30% with human marrow" (page 72, top of col. 2). Applicant also argues that Prockop also teaches the advantages of using **a more homogenous population of isolated mesenchymal stem cells over**

those isolated by adherence to plastic which is a crude procedure (page 72, cols. 1-2). Additionally, Prockop reference states "The adherent cells used as feeder layers for HSCs have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of nonadherent cells, but it is not clear whether they retain the potential to differentiate into bone, cartilage, and other mesenchymal cells, or whether they have differentiated into another and discrete phenotype because of their continue interaction with hematopoietic cells" (page 72, col. 3, bottom first paragraph). Lastly, Applicant argues that the isolated mesenchymal stem cells for use in the present invention are described as isolated and prepared using procedures described at least in US Patents 5,197,985, 5,226,917; and that this morphologically distinct homogenous isolated mesenchymals tem cell population is not isolated and prepared cell population using the crude plastic adherence methods described in Prockop.

Firstly, please note that **the bone marrow stromal cell population** taught by Wells et al. **is depleted of hematopoietic cells and macrophages, and containing mesenchymal stem cells or multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop**. This bone marrow stromal cell population falls within the broad scope mesenchymal stem cells isolated from human mesoderm tissue.

Secondly, the claims do not require the mesenchymal stem cells that are isolated from human mesoderm tissue (e.g., bone marrow) **are homogenous or purified by any particular method**, so that no T and B lymphocytes, macrophages and endothelial cells are found. Therefore, arguments related to the issue that the homogenous

mesenchymal stem cells of the present invention are isolated and prepared using procedures described at least in US Patents 5,197,985, 5,226,917, rather than the crude plastic adherence methods described in Prockop are irrelevant.

Thirdly, with respect to the above cited passages in the Prockop reference, one of the cited passages relates specifically to the cells described by Friedenstein that are heterogenous and are difficult to clone; and therefore it is irrelevant to the bone marrow stromal cell population of Wells et al. **that is depleted of hematopoietic cells and macrophages**. With respect to the other cited passage concerning whether adherent feeder layer cells retain the potential to differentiate into bone, cartilage, and other mesenchymal cells, or whether they have differentiated into another and discrete phenotype because of their continue interaction with hematopoietic cells; once again please note that the bone marrow stromal cell population of Wells et al is depleted of hematopoietic cells for any interaction. Furthermore, there is no factual evidence indicating that despite **having many of the characteristics of MSCs isolated by their adherence to plastic in the absence of nonadherent cells**, adherent feeder layer cells would not retain the potential to differentiate into bone, cartilage, and other mesenchymal cells. Moreover, it is noted that the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**" (page 13, lines

23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23).

Accordingly, amended claims 2 and 4-5 are still rejected under 35 U.S.C. 102(b) as being anticipated by Wells et al. as evidenced by Prockop, D.J. for the reasons set forth above.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633